

**IN THE CLAIMS**

Please amend the claims as follows:

1. (original) A method for the treatment of a disorder of the central nervous system (CNS) and/or the eye comprising administering to a subject a composition comprising a compound capable of modulating a target gene or gene product in a therapeutically effective amount, wherein said composition is administered outside the blood-brain and/or the blood-retina barriers.
2. (original) Use of a compound capable of modulating a target gene or gene product for the preparation of a pharmaceutical composition for the treatment of a disorder of the central nervous system (CNS) and/or the eye, wherein said composition is designed to be applied outside the blood-brain and/or blood-retina barriers.
3. (original) The method of claim 1 or the use of claim 2, wherein the disorder is related to the eye.
4. (original) The method or use of any one of claims 1 to 3, wherein said disorder is related to angiogenesis and/or neovascularization.
5. (original) The method or use of any one of claims 1 to 4, wherein said disorder is related to the retinal pigment epithelium (RPE), neurosensory retina AND/OR choriodea.
6. (original) The method or use of any one of claims 1 to 5, wherein said disorder is wet age-related macular degeneration (AMD) or diabetic retinopathy.
7. (original) The method or use of any one of claims 1 to 6, wherein the pharmaceutical composition is designated to be effective in (and applied to) the inner segment of the eye ball.
8. (original) The method or use of any one of claims 1 to 7, wherein the composition is in a form designed to be applied outside the retinal region of the blood-retina barrier.
9. (original) The method or use of any one of claims 1 to 8, wherein said compound is an inhibitor/antagonist of said target gene or gene product.

10. (original) The method or use of claim 9, wherein said antagonist/inhibitor inhibits the expression of a gene or the activity of a gene product involved in angiogenesis and/or neovascularization.
11. (original) The method or use of claim 9 or 10, wherein said antagonist/inhibitor is or is derived from an nucleic acid molecule, polypeptide, antibody, or a ligand binding molecule of said gene or gene product.
12. (original) The method or use of any one of claims 9 to 11, wherein said antagonist/inhibitor is a ribozyme, antisense or sense nucleic acid molecule to said gene or gene product.
13. (original) The method or use of any one of claims 9 to 12, wherein said antagonist/inhibitor substantially consists OF ribonucleotides.
14. (original) The method or use of claim 13, wherein said antagonist/inhibitor comprises substantially a portion of double-stranded oligoribonucleotides (dsRNA).
15. (original) The method or use of claim 14, wherein said dsRNA is between 21 and 23 nucleotides in length.
16. (original) The method or use of claim 14 or 15, wherein the dsRNA molecule contains a terminal 3'-hydroxyl group.
17. (original) The method or use of any one of claims 12 to 16, wherein the nucleic acid molecule represents an analogue of naturally occurring RNA.
18. (original) The method or use of claim 17, wherein the nucleotide sequence of the nucleic acid molecule differs from the nucleotide sequence of said gene or gene product by addition, deletion, substitution or modification of one or more nucleotides.
19. (original) The method or use of any one of claims 10 to 18, wherein said gene or a cDNA thereof comprises a nucleotide sequence or encodes an amino acid sequence selected from the group consisting of any one of SEQ ID NOS: 1 to 4.

20. (original) The method or use of any one of claims 1 to 19, wherein said compound is a nucleic acid molecule or encoded by a nucleic acid molecule and is designed to be expressed in cells of the CNS or eye.

21. (original) The method or use of any one of claims 1 to 20, wherein the composition is in a form designed to be introduced into the cells or tissue of the CNS or eye by a suitable carrier, characterized by the application occurring outside the blood-brain or blood-retina barriers.

22. (original) The method or use of any one of claims 1 to 21, wherein the composition is designed for systemic administration or for administration by iontophoresis.

23. (original) The method or use of any one of claims 1 to 21, wherein the composition is designed for retrobulbar application or as eye drops.

24. (original) A method of identifying and obtaining a nucleic acid molecule encoding a polypeptide involved in a disorder as defined in any one of claims 1 to 6 comprising the steps of :

(a) culturing a cell, tissue or non-human animal under stress conditions which lead to simulation of a pathological condition related to a CNS or eye disorder;

(b) isolating nucleic acids AND/OR proteins from a sample of said cell, tissue or animal;

(c) comparing the expression or activity profile of at least one of said nucleic acids and/or proteins with that of a corresponding non-treated cell, tissue or animal, and/or with that of a cell, tissue or animal, which has been treated under different stress conditions ;

(d) determining at least one nucleic acid and/or protein which is differentially expressed, whereby a change of expression or of the active amount of said at least one nucleic acid or activity of at least one of said proteins or an altered localization of the protein is indicative for its role in a disorder of the CNS or eye.

25. (original) The method of claim 24, wherein said stress condition is generated by an aberrant supply of the cell, tissue or animal culture conditions.

26. (currently amended) The method of claim 24 or [95] 25 wherein said aberrant supply is an aberrant supply of the interior segment of the eye.

27. (original) The method of any one of claims 24 to 26, wherein the method is a cell culture based method.

28. (original) The method of claim 27, wherein said cell is an RPE cell.

29. (original) The method of claim 28, wherein said cell is derived from an RPE derived cell line such as cell line ARPE-19.

30. (original) The method of any one of claims 24 to 26, wherein said method is performed with a non-human animal.

31. (original) The method of any one of claims 24 to 30, wherein said stress conditions comprise e. g. oxidative stress, hypoxic culture conditions, insufficient nutrition and/or supply with growth factors, change of pH-value and/or pathophysiological concentration of rod outer segments (ROS) and/or A2-E.

32. (original) The method of any one of claims 24 to 31, wherein expression of nucleic acids is analyzed with an expression array and/or realtime PCR.

33. (original) The method of any one of claims 24 to 32, wherein protein expression is analyzed with immunoblot or elisa assay, or 2D gel electrophoresis or maldi-tof.

34. (original) The method of claim 33, wherein antibodies are used which are specific for proteins involved in angiogenesis and/or neovascularization.

35. (original) The method of any one of claims 24 to 34, further comprising overexpression or inhibition of expression of the identified candidate nucleic acid or encoded polypeptide in said cell, tissue or animal for their capability of inducing a responsive change in the phenotype of said cell, tissue or animal, wherein said phenotype is related to a disorder of the CNS or eye.

36. (currently amended) The method of any one of claims 24 to 35, further comprising: (e) subjecting a cell of step (a) or secreted factors thereof, or cell lysates thereof, to endothelial cell cultures; and/or (f) analyzing cell proliferation, electrophysiological activity, DNA synthesis, out- growth of cells, cell migration, chemokinesis, chemotaxis, development of vessels, marker gene expression or activity, apoptosis and/or vitality.
37. (original) The method of any one of claims 24 to 36, wherein a sample of said cells are treated with an inhibitor specific for said candidate nucleic acid or encoded polypeptide; and further comprising determining. whether said cells, secreted factors thereof or cell lysates thereof have lost their capability of inducing said responsive change in said phenotype.
38. (original) The method of any one of claims 35 TO 37, wherein said phenotype is angiogenesis and/or neovascularization and/or degenerative retinal disorder.
39. (original) The method of claim 38, wherein said inhibitor is an inhibitor as defined in any one of claims 10 to 19.
40. (original) The method of any one of claims 24 to 39, further comprising identifying the sequence of said at least one nucleic acid and/or protein, and optionally identifying the corresponding encoding gene or cDNA thereof
41. (original) The method of claims 40, further comprising cloning said gene, cDNA or a fragment thereof.
42. (original) A nucleic acid molecule obtainable by the method of any one of claims 24 to 41.
43. (original) The nucleic acid molecule of claim 42 encoding a polypeptide involved in angiogenesis and/or neovascularization and/or retinal disorder.
44. (original) A nucleic acid molecule which specifically hybridizes to the nucleic acid molecule of claim 42 or 43, which encodes a mutated version of the protein which has lost its capability of inducing a responsive change in a phenotype as defined in any one of claims 35 to 38.

45. (original) The nucleic acid molecule of any one of claims 42 to 44, which is DNA.
46. (not entered)
47. (original) The nucleic acid molecule of any one of claim 42 to 64, which is derived from a mammal.
48. (original) The nucleic acid molecule of claim 47, wherein the mammal is mouse or human.
49. (original) A nucleic acid molecule of at least 15 nucleotides in length hybridizing specifically with a nucleic acid molecule of any one of claims 42 to 48 or with a complementary strand thereof.
50. (original) A vector comprising a nucleic acid molecule of any one of claims 42 to 49.
51. (original) The vector of claim 50, wherein the nucleic acid molecule is operatively linked to regulatory elements permitting expression in prokaryotic or eukaryotic host cells.
52. (original) A host cell comprising a vector of claim 50 or 51.
53. (original) The host cell of claim 52, which is a bacterial, fungal, plant or animal cell.
54. (original) The host cell of claim 53, which is a mammalian cell.
55. (original) The host cell of claim 54 which is an RPE cell or a neurosensory retina cell.
56. (original) A method for the production of a polypeptide capable of inducing a responsive change in a phenotype as defined in any one of claims 35 to 38 comprising culturing a host cell of any one of claims 52 to 55 under conditions allowing the expression of the polypeptide and recovering the produced polypeptide from the culture.

57. (original) A polypeptide encoded by a nucleic acid molecule of any one of claims 42 to 49 or obtainable by a method according to claim 56.
58. (original) An antibody specifically recognizing a polypeptide of claim 57.
59. (currently amended) A pharmaceutical composition comprising a nucleic acid molecule of any one of claims 42 to 49, or an nucleic acid molecule which is complementary to such a nucleic acid molecule, a vector of claim 50 or 51, a host cell of any one of claims 52 to 55, a polypeptide of claim 57 and/or an antibody of claim 58, and optionally pharmaceutically acceptable carrier.
60. (original) A diagnostic composition comprising a nucleic acid molecule of any one of claims 42 to 49, a vector of claim 50 or 51, a host cell of any one of claims 52 to 55, a polypeptide of claim 57 and/or an antibody of claim 58, and optionally suitable means for detection.
61. (original) A method for treating of a disorder as defined in any one of claims 1 to 6 comprising administering to the subject a pharmaceutical compositions of claim 59 in an effective dose.
62. (original) A method for detecting expression of a gene involved in a disorder as defined in any one of claims 1 to 6 comprising (a) obtaining mRNA from a cell ; (b) incubating the MRNA so obtained with a probe comprising a nucleic acid molecule of any one of claims 42 to 49 or a fragment thereof under hybridizing conditions; and (c) detecting the presence of MRNA hybridized to the probe.
63. (original) A method for detecting expression of a gene involved in a disorder as defined in any one of claims 1 to 6 comprising (d) obtaining a cell sample from the subject; (e) contacting the cell sample so obtained with an antibody of claim 58; and (f) detecting the presence of the antibody bound to the protein encoded by said gene.
64. (original) The method of claim 62 or 63 for the detection of the expression of a protein encoded by the nucleic acid molecule of claim 44.

65. (currently amended) A method for diagnosing in a subject to disorder as defined in any one of claims 1 to 6 or a predisposition to such disorder which comprises:

(a) isolating DNA from patient suffering from the disorder;

(b) digesting the isolated DNA of step (a) with at least one restriction enzyme;

(c) incubating the resulting gel with a probe comprising a nucleic acid molecule of any one of claims 42 to 49 or a fragment thereof labelled with a detectable marker ;

(d) detecting labelled bands on a gel which have hybridized to the probe as defined to create a band pattern specific to the DNA of patients of the disorder;

(e) preparing subject's DNA by steps (a) to (e) to produce detectable labeled bands on a gel; and

(f) comparing the band pattern specific to the DNA of patients of the disorder of step (e) and the subject's DNA of step (f) to determine whether the patterns are the same or different and to diagnose thereby the disorder or a predisposition to the disorder, if the patterns are the same.

66. (currently amended) A method for diagnosing a disorder as defined in any one of claims 1 to 6 or a predisposition to such a disorder comprising:

(a) analyzing a sample of nucleic acids of a subject by means of a diagnostic chip, primer extension, single nucleotide polymorphisms or sequencing comprising a nucleic acid molecule of any one of claims 42 to 49, and

(b) comparing the result with that OF A sample obtained from a patient suffering from the disorder, wherein the identity of expression profile and/or nucleotide sequence is indicative for the disorder.

67. (original) Use of an effective dose of a nucleic acid molecule of any one of claims 42 to 49, or a nucleic acid molecule which is complementary to such a nucleic acid molecule or a



vector of claim 50 to 51 for the preparation of a composition for treating, preventing and/or delaying a disorder as defined in any one of claims 1 to 6 in a subject by somatic gene therapy.

68. (currently amended) A method of determining whether a test substance has an effect on a nucleic acid molecule or polypeptide involved in a disorder as defined in any one of claims 1 to 6, comprising the steps:

(a) contacting a cell which expresses the polypeptide of claim 57 with a compound to be screened ; and

(b) determining if the compound modulates the expression or the activity of said polypeptide.

69. (original) The method of claim 68, wherein said polypeptide is expressed under the control of the GGTB-promoter.

70. (original) The method of claim 68 or 69, wherein the test substance is a chemotherapeutic agent.

71. (original) The method of any one of claims 68 to 70, wherein the test substance is a mixture of chemotherapeutic agents.

72. (original) The method of any one of claims 68 to 71, wherein said cell is derived from a single cell or a multi-cellular organism.

73. (original) The method of any one of claims 68 to 72, wherein said cell is a cell as defined in any one of claims 28, 29, 35 or 52 to 55.

74. (original) The method of any one of claim 68 TO 73, wherein preferably in the first screen said test substance is comprised in and subjected as a collection of test substances.

75. (original) The method of claim 74, wherein said collection of test substances has a diversity of about  $10^3$  to about  $10^5$ .

76. (original) The method of claim 74 or 75, wherein the diversity of said collection of test substances is successively reduced.

77. (original) The method of any one of claims 68 to 76, wherein said cell is comprised in a tissue or in a non-human animal.

78. (original) A method for producing a drug or prodrug for the treatment of a disorder as defined in any one of claim 1 to 6 comprising :

(a) synthesizing a test substance or a collection of test substances;

(b) subjecting said the test substance or collection of test substances to the method of any one of claims 68 to 77; and

(c) producing a compound identified as a modulator in step (b) or a derivative thereof.

79. (original) A test substance identified, isolated and/or produced by the method of any one of claims 68 to 78, wherein said test substance has hitherto not been known as a drug for the treatment of a disorder as defined in any one of claims 1 to 6.

80. (original) Use of a compound identified, isolated and/or produced by the method of any one of claims 68 to 78 for the preparation of a composition for the treatment of a disorder as defined in any one of claims 1 to 6.

81. (original) A method for the treatment of a disorder as defined in any one of claims 1 to 6, comprising administering a composition prepared according to the use of claim 80 or the method of claim 78 to a subject suffering from the disorder.

82. (original) A chip comprising a solid support and attached thereto one or more of the nucleic acid molecules of any one of claims 42 to 49.

83. (original) A kit for use in the method of any one of claims 24 to 41 or 62 to 78 comprising a chip of claim 82 or other means for the detection of expression and/or activity of a nucleic acid molecule of any one of claims 42 to 49 or a polypeptide of claim 58.

84. (original) Use of a compound identified, isolated and/or produced by the method of any one of claims 68 to 78 as a lead compound in drug discovery and preparation of drugs or prodrugs.
85. (original) Use of a nucleic acid molecule of any one of claims 42 to 49 or of a polypeptide of claim 57 for the validation of test substances, lead compounds, drugs and prodrugs for the treatment of a disorder as defined in any one of claims 1 to 6 or for the identification and isolation of downstream genes, which respond to modulation of a gene comprising a nucleic acid molecule of any one of claims 42 to 49 or its encoded gene product.
86. (original) A transgenic non-human animal which displays an aberrant expression or activity of the polypeptide of claim 57.
87. (currently amended) The non-human animal of claim 86, wherein said animal reproduces a disorder as defined in any one of claims 1 to 6.
88. (original) The animal of claim 86 or 87 which is a mammal.
89. (original) Use of a transgenic non-human animal of any one of claims 86 to 88 for a process in drug discovery for the treatment of a disorder as defined in any one of claims 1 to 6.
90. (original) A pharmaceutical composition for use in the treatment of a disorder as defined in any one of claim 1 to 6 comprising one or more double-stranded oligoribonucleotides (dsRNA), which mediate an RNA interference of the corresponding mRNA of one or more nucleic acid molecules of any one of claims 42 to 49, and optionally a pharmaceutically acceptable carrier.
91. (new) The nucleic acid molecule of claim 45 which is cDNA.